

Attorney Docket No.: F7590(V)
Serial No.: 10/072,570
Filed: February 8, 2002
Confirmation No.: 1952

REMARKS

Claim Rejections – 35 USC § 103

Claims 11-16, 19-21, 23, 24, 27 and 29 were rejected under 35 USC §103(a) as being unpatentable over Manzoni et al (Production of Statins by filamentous Fungi, 1999), Zhang et al (US 6,046,022) and Chaihorsky (US 5,670,632). Applicants respectfully request the Examiner to reconsider and withdraw the rejection based on the following remarks.

Applicants' invention is directed to margarine, dressing, sweets, cereal bar, breakfast cereal or beverage which includes an ethanol or edible oil extract of a fermentation product of *Monascus ruber* fungus. The fermentation product is produced under conditions which yields a low color as measured by a Hue a* value less than 20. The fermentation substrate includes at least 50% whole soybeans, crushed whole soybeans, soy protein, soy milk or soy flakes.

Applicants discovered that the fermentation of soy ingredients (e.g., crushed soybeans) with *Monascus ruber* contained a collection of beneficial "soy actives" (page 8, lines 15-17) but in contrast to prior art fermentation products of other monascus strains and substrates (e.g., rice fermented with *Monascus purpureus went*), applicants' fermentation product had a low color which allowed the "soy actives" to be easily extracted with ethanol or vegetable oil, and incorporated directly in a variety of foods without affecting their normal color. Thus, applicants found a practical way to

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incorporate a collection of natural and beneficial ingredients in foods without the expense of adding highly purified individual components.

Applicants respectfully submit that the combination of references cited by the Examiner would not have reasonably led a person of ordinary skill in the art to applicants' invention for the following reasons.

Firstly, applicants submit that a person of ordinary skill in the art would have been reasonably dissuaded by Manzoni et al from using *Monascus ruber* to produce statins by fermentation of soy ingredients.

Manzoni et al screened 14 strains of *Monascus* and 7 strains of *Aspergillus* for the production of lovastatin, pravastatin, mevastatin and monacolin. The growth medium was supplemented with 3% whole or defatted soybean flour. *M. ruber* was mentioned as one of the *Monascus* strains tested and not specifically mentioned again in the article. All extracts were carried out with ethyl acetate. Manzoni et al are silent regarding the color of any extract.

Manzoni et al reported that only 10 of the 14 *Monascus* strains produced lovastatin and only 8 of the 14 *Monascus* strains produced monacolin. Strains that were active were not identified. Only *Monascus paxii* had notable activity for all statins and was the only *Monascus* strain that produced pravastatin

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Manzoni et al found that *Aspergillus terreus* strains in contrast to *Monascus* produced much higher yields of statins. The overall conclusions reached by Manzoni et al (page 255, column 2, next to last paragraph) was "From all the results of these preliminary screening experiments it can be concluded that lovastatin and pravastatin can be produced in appreciable yields by *Aspergillus terreus* strains employing the defatted soybean flower medium." [emphasis added]

Thus, Manzoni et al essentially teaches that *M. ruber* is unremarkable in its ability to produce statins. There is no evidence in Manzoni et al that *M. ruber* would have produced any level of statins using the substrates recited in applicants' claims, because *M. ruber* could well have fallen into the group of *Monascus* strains that were inactive. In fact, based on Manzoni et al, it is entirely reasonable to conclude that the artisan would not have been motivated to select any *Monascus* strain but rather to have selected *Aspergillus* because Manzoni et al teach that *A. terreus* provided much higher yields than even the best *Monascus* strain, *M. paxii*.

Zhang et al. was relied upon for its teaching "a method of fermenting red rice with *Monascus* in order to formulate a dietary supplement or medicament for the treatment of high cholesterol in humans" (April 23 Office Action page 4). *Monascus purpureus* went was disclosed as the preferred *Monascus* strain.

Applicants' are aware of the use of fermented rice, "red rice", as a traditional Chinese medicine (page 2, lines 26-30) and as a food supplement (page 3, lines 8-11). However, as applicants' note on page 3, line 25 to page 4, line 2, this material is highly

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colored and is of limited use in a many food products because of discoloration of the food product. In fact, one of the key objectives of applicants' invention is an economical fermentation product that provides statins and other soy actives in sufficient quantities which are suitable for inclusion in foods without sensory negatives. Zhang et al. offer no guidance as to how this could have been achieved, or suggest any alternative substrate/fungi combination that would have produced adequate levels of soy actives in an extract widely suitable for foods, or even recognized the problem which applicants have solved.

Chaihorsky et al was relied upon for its teaching that "isoflavones have been isolated from soybean plants for use as dietary supplements and include isoflavones in a glucone form such as genistein and genestin" and that "typically the isoflavones are eluted by polar solvents such as methanol or ethanol". [emphasis added].

Chaihorsky et al are in fact silent about extractions of any fermentation products of soy. Ethanol is used an eluent in a chromatographic separation of the products of soybean plant extracts, principally 7-glycosyl-isoflavones, i.e., glycosilated isoflavones (claim 1 and column 2, line 40). The actual extraction solvent taught by Chaihorsky et al is in fact an aqueous alkali solution (column 1, lines 32-34).

Setting aside that Chaihorsky et al teach aqueous alkali extraction, the key soy plant-extract separated by chromatography according to Chaihorsky et al is 7-glycosyl-isoflavones (claim 1 and column 2, line 40). In contrast, applicants have found that fermentation according to their invention, converts glycosylated isoflavones

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into the corresponding non-glycosylated isoflavones, which are more beneficial (Page 11, lines 6-9). For instance, the amount of genistein and daidzein is increased in the fermented soy compared to the non-fermented soy. Surprisingly this advantageous conversion occurs simultaneously with the production of statin. (Page 11, lines 6-12). Thus, a person of ordinary skill in the art following the teachings of Chaihorsky et al would have been dissuaded from utilizing applicants' fermentation extracts because 20-80% of the isoflavons are in a non-glycosylated form (Page 11, line 18-19).

In summary, Manzoni et al, Zhang et al and Chaihorsky et al are directed to entirely different technical problems from applicants'. Applicants respectfully submit that absent a disclosure of the type food products, the type and derivation of the low-color health-benefit extracts recited in applicants' claims, and the significant teachings away from these elements, the references do not present a *prima facie* case of obviousness.

Claim 22 and 28 were rejected under 35 USC §103(a) as being unpatentable over Manzoni et al (Production of Statins by filamentous Fungi, 1999), Zhang et al (US 6,046,022) Chaihorsky (US5,670,632) in further view of Zilliken (US 4, 218,489). Applicants respectfully request the Examiner reconsider and withdraw this rejection based on the following remarks.

Applicants' claim 22 specifies that the fermentation product is formed by fermenting a substrate comprising more than 50% of soy ingredients with statins producing fungus in the presence of more than 10% of a vegetable oil.

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Applicants' claim 28 specifies that the edible oil used in the extraction is vegetable oil.

Manzoni et al, Zhang et al, Chaihorsky (US5,670,632) have already been discussed.

Zilliken was relied on for its teaching of "antioxidant food composition with isoflavones (abstract) and "that vegetable oils protect isoflavones or their extracts from oxidation" (column 7, lines 46-51). The Examiner further asserted that "one would have been motivated to include vegetable oil because it protects food from oxidation thus increasing antioxidant effectiveness"

Applicants respectfully submit that the Examiner has misconstrued the cited passage from Zilliken (column 7, lines 46-51) which reads in pertinent part:

"Oils protected against oxidation in the manner described herein with respect to palm oil or corn oil include Soybean oil, peanut oil, safflower oil, olive oil, sunflower oil, cottonseed oil and the like. Fats including the natural fats, lard, and synthetic fats, such as are derived from hydrogenated vegetable oils, are similarly protected against oxidation in accordance with this invention by incorporating either the two isoflavones or extracts thereof in an amount in the range ofor by incorporating therein the ergostadienol or extracts thereof in addition to the isoflavones"

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Thus, it is the isoflavones which are the antioxidants and are incorporated in the vegetable oils to protect the vegetable oil from oxidation. Consequently, there would have been no motivation for one to incorporate vegetable oil to protect food from oxidation as the Examiner asserted.

Zilliken is in fact silent about carrying out any fermentation process in the presence of vegetable oil and is silent about extracting any product with vegetable oil.

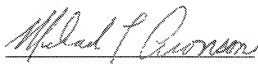
Since Zilliken does not remedy the shortcomings of the combination of Manzoni et al, Zhang et al and Chaihorsky et al as a 103(a) reference against claim 19 nor disclose the elements of claims 22 and 28, the combination of references do not present a *prima facie* case of obviousness.

In light of the above remarks, applicants respectfully request that that the application be allowed to issue without further delay.

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If a telephone conversation would be of assistance in advancing prosecution of the subject application, applicants' undersigned agent invites the Examiner to telephone him at the number provided.

Respectfully submitted,

A handwritten signature in cursive script, reading "Michael P. Aronson", written in dark ink.

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